

### **REMARKS**

Claims 1, 7, 8, 10-15, 20 and 21 are pending in the instant application. Applicants have hereinabove cancelled claims 9 and 10 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a future application. In addition, applicants have hereinabove amended claims 1 and 11-15. Support for the amendments to the claims may be found, *inter alia*, in the subject specification as follows: claims 1 and 11-15: original claim 2 and Example 1. The remaining changes to the claims merely introduce minor grammatical and format changes. This Amendment does not involve any issue of new matter. Therefore, entry of this Amendment is respectfully requested such that claims 1, 7, 8, 11-15 and 20-21 will be pending and under examination.

### **Claim Rejections Under 35 U.S.C. §103(a)**

#### **Stephenson et al. (US2004/0034083) in view of Fahn et al.**

The Examiner rejected claims 1, 7, 8, 10-15 and 16-21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Stephenson et al. (US2004/0034083) in view of Fahn et al. (cited in IDS). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to administer rofecoxib and pergolide in the treatment of Parkinson's disease because such a combination is allegedly taught in Stephenson et al. and that one of skill in the art would have been motivated to administer such a combination in patients with Parkinson's disease. The Examiner alleges that the invention would have been prima facie obvious to one skilled in the art at the time it was made.

In response, applicants previously cancelled claims 16-19 without prejudice or disclaimer. In addition, applicants have hereinabove cancelled claim 10 without prejudice or disclaimer. Therefore, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that a prima facie case of obviousness does not exist with respect to any of the pending claims.

Claims 1, 7, 8, 11-15, 20 and 21 provide methods for treating or relieving the symptoms of Parkinson's disease in a patient in need thereof comprising administering to said patient a combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, in therapeutically effective amounts. In preferred embodiments, the COX-2 inhibitor is rofecoxib, the dopaminergic agent is pergolide and the monoamine oxidase agent is selegiline.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to the claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Stephenson et al. when combined with Fahn et al., fail to provide a motive to combine and a reasonable expectation of success.

Stephenson et al. does not teach or suggest the specific tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, to treat or ameliorate the symptoms of Parkinson's disease. Instead, Stephenson et al. provide a laundry list of COX-2 inhibitors that may be combined with a laundry list of second drugs to treat Parkinson's disease. Stephenson et al. provide no guidance as to what combination would treat Parkinson's disease as there are no examples except those examples that list all known COX-2 inhibitors and all possible second drugs. Thousands of combinations are possible, if not more, based on the description set forth in Stephenson et al. Those of skill in the art know that each combination of drug class is unique. Therefore, one of skill in the art would not have had any expectation that applicant's tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, would successfully treat Parkinson's disease (as applicants show in Example 1) based on Stephenson et al. .

Likewise, Fahn et al. does not teach or suggest a combination of a COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase, to treat or ameliorate the symptoms of Parkinson's disease. Nowhere does Fahn et al. mention the use of a COX-2 inhibitor to be used in combination with a dopaminergic agent and a monoamine oxidase, to treat Parkinson's disease.

According to the MPEP 2143.01,

"[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create applicants' claimed invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to use a tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, to treat or ameliorate the symptoms of Parkinson's disease. (*In re O'Farrell*, 853 F.2d 894, 903 (Fed Cir. 1988)). Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

In view of the above remarks, applicants maintain that claims 1, 7, 8, 11-15, 20 and 21 satisfy the requirements of 35 U.S.C. 103(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Teismann et al. (cited in IDS) in view of Factor et al.

The Examiner rejected claims 1, 7, 8, 12-15 and 21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Teismann et al. (cited in IDS) in view of Factor et al. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to administer rofecoxib and pergolide in the treatment of Parkinson's disease because such a combination is allegedly taught in Teismann et al. and Factor et al. and that one of skill in the art would have been motivated to administer such a combination in patients with Parkinson's disease. The Examiner alleges that the invention would have been prima facie obvious to one skilled in the art at the time it was made.

In response, applicants respectfully traverse, and maintain that a prima facie case of obviousness does not exist with respect to any of the pending claims.

Claims 1, 7, 8, 12-15, and 21 provide methods for treating or relieving the symptoms of Parkinson's disease in a patient in need thereof comprising administering to said patient a tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, in therapeutically effective amounts. In preferred embodiments, the COX-2 inhibitor is rofecoxib, the dopaminergic agent is pergolide and the monoamine oxidase agent is selegiline.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to the claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Teismann et al. when combined with Factor et al., fail to provide a motive to combine and a reasonable expectation of success.

Teismann et al. does not teach or suggest the specific tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, to treat or ameliorate the symptoms of Parkinson's disease. Instead, Teismann et al. only teach the use of rofecoxib to treat Parkinson's disease in mice. Teismann et al. provide no guidance as to what combination would treat Parkinson's disease as there are no examples or suggestion to combine drugs to treat Parkinson's disease.

Likewise, Factor et al. does not teach or suggest a tripartite combination of a COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase, to treat or ameliorate the symptoms of Parkinson's disease. Nowhere does Factor et al. mention the use of a COX-2 inhibitor to be used in combination with a dopaminergic agent and a monoamine oxidase, to treat Parkinson's disease.

According to the MPEP 2143.01,

"[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create applicants' claimed invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to use a tripartite combination of a COX-2 inhibitor, a dopaminergic agent, and a monoamine oxidase agent, to treat or ameliorate the symptoms of Parkinson's disease. (*In re O'Farrell*, 853 F.2d 894, 903 (Fed Cir. 1988). Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede

exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

In view of the above remarks, applicants maintain that claims 1, 7, 8, 12-15 and 21 satisfy the requirements of 35 U.S.C. 103(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Teismann et al. (cited in IDS) in view of Factor et al. and further in view of Heinonen et al.

The Examiner rejected claims 10 and 21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Teismann et al. (cited in IDS) in view of Factor et al. and further in view of Heinonen et al. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to administer a combination of selegiline, rofecoxib and pergolide in the treatment of Parkinson's disease because each compound is taught individually in Teismann et al., Factor et al. and Heinonen et al. and that one of skill in the art would have been motivated to administer such a combination in patients with Parkinson's disease. The Examiner alleges that the invention would have been prima facie obvious to one skilled in the art at the time it was made.

In response, applicants have hereinabove cancelled claim 10 without prejudice or disclaimer. Therefore, the rejection thereof is now moot.

In response to the Examiner's rejection of the 21, applicants respectfully traverse, and maintain that a prima facie case of obviousness does not exist with respect to any of the pending claims. Claim 21 provides A method of treating Parkinson's disease in a human in need of such treatment according to claim 1 comprising: the administration to a human in need of such treatment of an antiparkinson therapeutic amount of pergolide, an antiparkinson therapeutic amount of selegiline and an anti-inflammatory effective amount of rofecoxib (VIOXX®).

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to the claim. First, the cited references, when combined, must teach or suggest

every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Teismann et al. when combined with Factor et al. and Heinonen et al., fail to provide a motive to combine and a reasonable expectation of success.

Teismann et al. does not teach or suggest the specific tripartite combination of pergolide, selegiline and rofecoxib. Instead, Teismann et al. only teach the use of rofecoxib to treat Parkinson's disease in mice. Teismann et al. provide no guidance as to what combination would treat Parkinson's disease as there are no examples or suggestion to combine drugs to treat Parkinson's disease.

Likewise, Factor et al. does not teach or suggest a tripartite combination of pergolide, selegiline and rofecoxib, to treat Parkinson's disease. Nowhere does Factor et al. mention the use of a rofecoxib to be used in combination with pergolide and selegiline to treat Parkinson's disease.

Heinonen et al. also does not teach or suggest a tripartite combination of pergolide, selegiline and rofecoxib, to treat Parkinson's disease. Nowhere does Heinonen et al. mention the use of a rofecoxib to be used in combination with pergolide and selegiline to treat Parkinson's disease.

According to the MPEP 2143.01,

"[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create applicants' claimed invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to use a tripartite combination of rofecoxib, pergolide and selegiline to treat Parkinson's disease. (*In re O'Farrell*, 853 F.2d 894, 903 (Fed Cir. 1988)). Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

In view of the above remarks, applicants maintain that claim 21 satisfies the requirements of 35 U.S.C. 103(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Teismann et al. (cited in IDS) in view of Factor et al. and further in view of Fahn et al.

The Examiner rejected claim 11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Teismann et al. (cited in IDS) in view of Factor et al. and further in view of Fahn et al. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to treat Parkinson's disease wherein the Parkinson's disease is Hoehn & Yahr Stage I-III Parkinson's disease by administering rofecoxib and pergolide and that one of skill in the art would have been motivated to administer such a combination in patients with Parkinson's disease. The Examiner alleges that the invention would have been prima facie obvious to one skilled in the art at the time it was made.

In response, applicants respectfully traverse, and maintain that a prima facie case of obviousness does not exist with respect to any of the pending claims. Claim 11 provides A method for the treating Hoehn & Yahr Stage I-III Parkinson's disease, which method



comprises administration to a patient in need of such treatment of an amount of a selective COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase agent, such that together they provide effective treatment.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to the claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Teismann et al. when combined with Factor et al. and Fahn et al., fail to provide a motive to combine and a reasonable expectation of success.

Teismann et al. does not teach or suggest the specific tripartite combination of a selective COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase agent. Instead, Teismann et al. only teach the use of rofecoxib to treat Parkinson's disease in mice. Teismann et al. provide no guidance as to what combination would treat Parkinson's disease as there are no examples or suggestion to combine drugs to treat Parkinson's disease.

Likewise, Factor et al. does not teach or suggest a tripartite combination of a selective COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase agent, to treat Parkinson's disease. Nowhere does Factor et al. mention the use of a rofecoxib to be used in combination with pergolide and selegiline to treat Parkinson's disease.

Furthermore, Fahn et al. does not teach or suggest a combination of a COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase, to treat or ameliorate the symptoms of Parkinson's disease. Nowhere does Fahn et al. mention the use of a COX-2 inhibitor to be used in combination with a dopaminergic agent and a monoamine oxidase, to treat Parkinson's disease.

According to the MPEP 2143.01,

"[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create applicants' claimed invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to use a tripartite combination of a selective COX-2 inhibitor, a dopaminergic agent and a monoamine oxidase agent, to treat Parkinson's disease. (*In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

In view of the above remarks, applicants maintain that claim 11 satisfies the requirements of 35 U.S.C. 103(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

### **Summary**

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection, and earnestly solicit allowance of the pending claims.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the large entity amount of such fee to Deposit Account No. 13-2755 referencing attorney docket number 21309YP.

Respectfully submitted,

By /Maria V. Marucci, Reg. # 59895/  
Maria V. Marucci  
Reg. No. 59,895  
Attorney

MERCK & CO., INC.  
P.O. Box 2000  
Rahway, New Jersey 07065-0907  
(732) 594-1637